Assistant Commissioner for Patents

REMARKS

The Applicants have amended claims 1, 5, 6, 7, 8 and 9 to 19 without prejudice to pursue the deleted subject matter in a divisional or continuation application. The Applicants have amended claims 1, and 5 to 10 to delete the term "pro" which appears in the first line of each of the claims. This amendment was done to better define the invention and does not introduce new matter. The Applicants have added claim 21 directed to *trans*CH_3-CH_2-CH=CH-CH_2-CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2. These amendments do not introduce new matter and are fully supported by the application as originally filed. The Applicants have canceled claims 2,3, 4 and 20 without prejudice to pursue the deleted subject matter in a divisional or continuation application. The Applicants respectfully request the Examiner to enter these amendments to the application.

The Applicants have enclosed a copy of the Exhibits cited in the Declaration of Dr. Brazeau sent under cover of the September 15, 1997, response.

The Examiner has withdrawn the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 112. The only outstanding rejections are under 35 U.S.C. § 103.

Rejections under 35 U.S.C. § 103

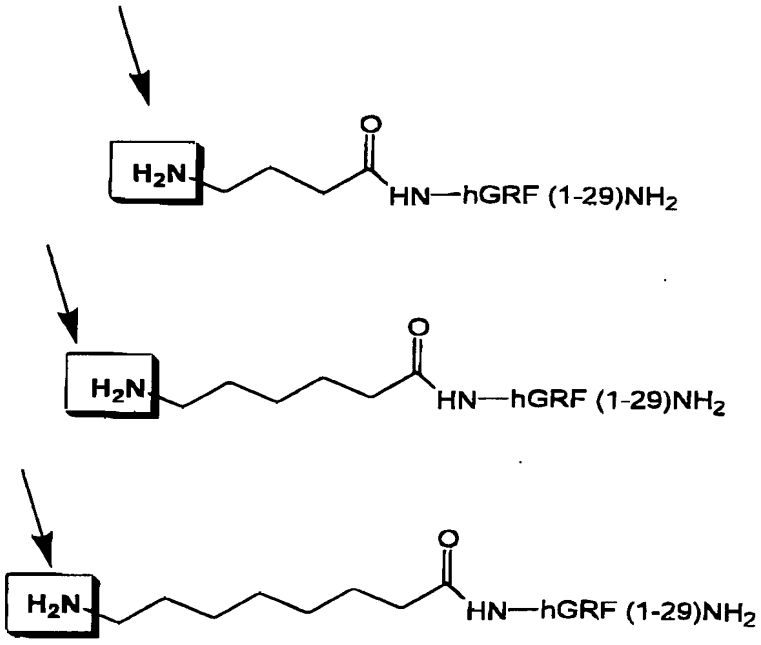
The Examiner has rejected claims 1-11, 13, 14 and 18-20 as being unpatentable over Gaudreau *et al.* in view of Coy *et al.* and in further view of Felix *et al.* The Applicants respectfully disagree but, in order to advance prosecution,

Assistant Commissioner for Patents

have amended the claims to better distinguish the claimed invention from Gaudreau *et al.* and Coy *et al.* The Applicants clearly believe that the invention as claimed cannot be considered obvious in view of the cited references based on the following grounds.

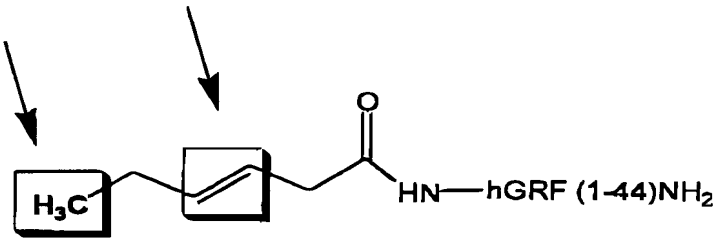
The amended claims are now directed to a chimeric GRF analog with increased biological potency which comprises an N-anchored hydrophobic tail of 5 to 7 carbon atoms which comprises at least one double bond. The hydrophobic tail is not terminated by a nitrogen atom as in Gaudreau *et al.* but rather by a carbon atom. Furthermore, the hydrophobic tail of the chimeric GRF analog with increased biological potency of the present invention comprises at least one double bond. None of Gaudreau *et al.* and Coy *et al.* comprises a double bond.

The compounds of Gaudreau *et al.* can be represented as follows:



Assistant Commissioner for Patents

A preferred embodiment of the chimeric GRF analog with increased biological potency of the present invention can be represented as follows:



TT-9507

The Applicants wish to point that the chimeric GRF analogs with increased biological potency of the present invention are structurally different from the compounds of Gaudreau *et al.* Furthermore, the chimeric GRF analogs with increased biological potency of the present invention have surprisingly interesting biological properties. For example, natural GRF, which was first described in 1982, has a half-life of 4 minutes in blood and is not a suitable drug, because of its low activity *in vivo*. The chimeric GRF analogs with increased biological potency of the present invention have longer effect in blood.

The introduction of double bond was not suggested or taught by Gaudreau. In fact, Gaudreau teaches away from the present invention. Page 1867 of the Gaudreau *et al.* paper states that:

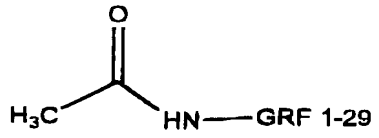
> *"N-terminus elongation of hGRF(1-29)NH_2 by 4, 6 or 8 carbon atoms (6-8) to increase peptide hydrophobicity, while preserving the α-amino function, generated analogues with a similar (7) or reduced affinity (6,8). Altogether, these results indicate that modification at the N-terminus of hGRF(1-29)NH2 do not*

Assistant Commissioner for Patents

constitute a suitable approach to increase receptor affinity" (emphasis added)

In the rejection, the Examiner combined the Gaudreau *et al.* reference with the Coy *et al.* reference. There is no teaching in any of the references that adding an unsaturated hydrophobic tail at the N-terminal of GRF would lead to a compound that is more active than natural GRF and has a longer half-life.

The Coy *et al.* paper evaluated the biological activity of a compound of the following formula:



The Applicants wish to point to the Examiner that the Coy *et al.* compound and the chimeric GRF analogs with increased biological potency of the present invention are totally different entities.

The compound of Coy *et al.* is a GRF peptide substituted with a 2 carbon acyl group which is polar and hydrophilic. The chimeric GRF analogs with increased biological potency of the present invention are substituted with a 5-7 carbon unsaturated chain which is non-polar and hydrophobic.

The introduction of a double bond was not suggested or taught by Coy. The introduction of a 5-7 carbon unsaturated hydrophobic tail was not suggested or taught by Coy.

The Applicants clearly believe that, having in hand the publications of Gaudreau *et al.* and Coy *et al.*, the skilled artisan would not obtain the chimeric GRF analogs with increased biological potency of the present invention without using inventive skill. The proper standard for obviousness is whether a skilled artisan having in hand the cited references

Assistant Commissioner for Patents

would have been led to the claimed invention without using inventive ingenuity.

The Examiner has also rejected the claims on the basis of the publication of Gaudreau *et al.* in combination with various references. As demonstrated above, the Gaudreau *et al* references is not relevant to the claimed invention. The references that the Examiner combined with Gaudreau *et al.* only teach the general state of the art. In view of the above arguments, the Applicants therefore believe that the amended claims cannot be considered obvious in view of the cited references. Withdrawal of the rejection is thereby requested.

Double-patenting rejection

The claims have also been rejected with a provisional obviousness-type double patenting rejection over copending application serial No. 08/702,113. Any grounds which may exist for this rejection are obviated by the accompanying Terminal Disclaimer under 37 C.F.R. Section 1.321, executed by an officer of the Assignee of the instant application. Reconsideration and withdrawal of the obviousness-type double patenting rejection are respectfully requested.

As the above-indicated amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

It is submitted therefore, that the claims are in condition for allowance. Reconsideration of the rejections is requested. Allowance of all claims at an early date is solicited.

In the event that there are any questions concerning this response or the application in general, the Examiner is

Assistant Commissioner for Patents

respectfully urged to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,
MICHEL IBEA ET AL.

By: _____
J.D. Evans
Registration No. 26,269

Date: March 25, 1998

EVENSON, MCKEOWN, EDWARDS
& LENAHAN, P.L.L.C.
1200 G Street, N.W., Suite 700
Washington, D.C. 20005
Telephone: (202) 628-8800
Facsimile: (202) 628-8844